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IL-17 in protective immunity to intracellular pathogens

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The identification of a new T-cell subset referred to as T helper 17 (Th17) cells and its role in protective immunity against extracellular bacterial infections is well established. In contrast, initial studies suggested that the IL-23-IL-17 pathway was not required for protection against intracellular pathogens such as mycobacterial infections. However, recent studies demonstrate that Th17-IL-23 pathway may play a crucial role in protective immunity against other intracellular pathogens by regulating the innate and adaptive immune responses. The current outlook on the role of IL-23-IL-17 pathway in protective immunity to intracellular pathogens is discussed here.

Key words: IL-17, Th1, Th17, intracellular pathogens

Abbreviations: APC, antigen presenting cell; IFN, interferon; IL, interleukin; Th, T helper cell; KO, knock out

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Introduction

Until recently, effector CD4 T helper cells have been classified into T helper1 (Th1) and T helper2 (Th2) effectors[1] based on the signature cytokines that they produce. Th1 effector cells produce the cytokine Interferon-gamma (IFNγ) and are known to regulate immunity against intracellular infections, whereas Th2 effector cells produce the cytokines Interleukin (IL)-4, IL-5 and IL-13 and are known to mediate humoral immunity against parasite infections. Recent functional evidence has changed the Th1/Th2 cell dichotomy to include a new T cell subset referred to as T helper 17 (Th17) cells.[2,3] Studies suggest that the IL-23-Th17 pathway has evolved to confer protective immunity against extracellular bacterial infections.[4-6] In contrast, initial studies by us and others suggested that the IL-23-Th17 pathway was not critical for protection against intracellular pathogens such as *Mycobacterium tuberculosis*,[7] *and M. bovis* BCG.[8] However, recent studies demonstrate that IL-23-IL-17 pathway may in fact play a crucial role in protective immunity against other intracellular pathogens. The current consensus on the role of IL-23-IL-17 pathway in protective immunity to intracellular pathogens is discussed here.

IL-17-producing Cells and Th17 Cells in Intracellular Infectious Diseases

Th17 CD4 T cells have been characterized to produce the cytokines IL-17A (IL-17) and IL-17F, as well as IL-21 and IL-22 (reviewed in ref. 9). The differentiation of Th1 or Th17 cells occurs following exposure to APC-derived polarizing cytokines such as IL-12,[10] for Th1 cells and TGFβ, IL-6, IL-1β and IL-23 for Th17 cells.[2,3,11-13] Although IL-23 is not required for generation of murine Th17 cells in vitro,[11] it is critical for in vivo Th17 responses in mice.[4,6,7,14-16] In contrast, generation of human Th17 cells is dependent on IL-23,[13,17] IL-1β,[13,18,19] TGFβ[17] and IL-6.[19] These polarizing cytokines further induce the expression of the transcription factors T-bet or RORγt and RORα for Th1 and Th17 differentiation respectively.[20,21] Dendritic cells activated by signals from Pathogen Associated Recognition Receptors (PRRs) recognize components of intracellular pathogens such as *M. tuberculosis*,[22] *Francisella tularensis*[23] and *Salmonella enterica*[24] and induce the production of polarizing cytokines and drive generation of Th17 responses. Consistent with these findings, Th17 cells are induced following infection with *M. tuberculosis*,[7] *F. tularensis*[15,25]

and *Chlamydia muridarum*,[26] suggesting a role for Th17 cells in immunity against intracellular pathogens.

Although most of the recent studies have focused on IL-17 produced by CD4 αβ T cells, γδ T cells are potent producers of IL-17 during the early immune response following intracellular infections. In murine models of infection with *M. tuberculosis,*[27] *M. bovis* BCG,[8] *S. enterica*,[28] *S. typhimurium*,[29] *Listeria monocytogenes*[30,31] and *F. tularensis* LVS,[15,25] γδ T cells are a major producer of IL-17. Consistent with animal models, γδ T cells are also a major source of IL-17 in human tuberculosis patients.[32] Furthermore, a αβ-TCR$^+$ CD4$^-$CD8$^-$ T-cell population that produces IL-17 in response to *L. monocytogenes*[30] and *F. tularensis* LVS infection[30,33] has been documented. These studies suggest that IL-17 production by innate cells may function as a bridge between innate and adaptive immunity and contribute to protective immunity against intracellular pathogens.

IL-17 is not Critical for Overall Protection, but Mediates Inflammatory Responses Against Some Intracellular Pathogens

A clear role for IL-17 in generation of chemokine responses, induction of antimicrobial proteins and recruitment for neutrophils for control of extracellular pathogens has emerged (reviewed in ref. 34). In contrast, early studies suggested that the Th17 effector cytokines were not required for overall protection against some intracellular infections.[7,8] For example, although the absence of the IL-23/IL-17 axis resulted in reduced inflammation following *M. tuberculosis* pulmonary infections,[7] IL-17Receptor Knock Out (IL-17RKO)[5] and IL-23KO[7] mice were not more susceptible than wild-type control mice to *M. tuberculosis* pulmonary infection. However, IL-23 was shown to provide some protective immunity in the absence of functional IL-12 during murine tuberculosis.[7] Also in pulmonary infection with *M. bovis* BCG, absence of IL-17 did not impact overall survival or susceptibility to infection, but impacted the formation of granulomas in the lung.[8,35] Interestingly, in *M. bovis* BCG infected mice, absence of IL-17 also resulted in reduced generation of IFNγ-producing Th1 cells and impaired neutrophil recruitment to the lungs, without increase in bacterial burdens.[8] In contrast, there were no defects in Th1 responses in the absence of IL-23 in a systemic *M. bovis* BCG infection model.[36] These murine models suggest that in the presence of functional IL-12/Th1 pathway, IL-23/Th17 pathway is not crucial for primary protection against mycobacterial infections, but may play a role in granuloma formation and inflammation[7,8] (**Fig. 1A**). Therefore, although mycobacteria-specific human Th17 cells have been described,[37,38] the actual role of the Th17 cells during human mycobacterial infections is still not completely understood. In contrast, in murine models, Th17 cells may have an important role to play in vaccine-induced immunity against mycobacterial infections.[14]

Similarly, infection with *S. enterica* in IL-23KO mice did not result in increased susceptibility,[39] suggesting that IL-23/IL-17 pathway is not critical for protection against this intracellular pathogen in mouse models.

IL-17 is Required for Generation of Th1 Responses and Protective Immunity Against some Intracellular Pathogens

Pulmonary infection in mice with the intracellular bacterium *F. tularensis* LVS induced Th17 cells,[40] suggesting a role for IL-17 in protective immunity against this pathogen. Accordingly, the absence of IL-23/IL-17 pathway in mice resulted in increased susceptibility to pulmonary tularemia and correlated with decreased Th1 responses.[15] The mechanism by which IL-17 regulates the Th1 pathway appears to be via induction of IL-12 and IFNγ in APCs. Following IL-17 stimulation, both DCs and macrophages produced IL-12 and IFNγ and regulated downstream immune responses.[15] For example, IL-17 dependent-DC-derived IL-12 was able to drive the differentiation of naive T cells into Th1 cells, while IL-17-dependent macrophage-derived IFNγ was able to activate macrophages for control of intracellular Francisella.[15] Although until recently, non-hematopoietic cells such as fibroblasts and epithelial cells were thought to be the primary responders to IL-17,[41] more recent evidence suggests that macrophages and dendritic cells express the receptors for IL-17 (IL-17RA and IL-17RC), and can respond to IL-17 and produce cytokines and chemokines.[15,42] These data suggest that IL-17 responses can regulate the induction and generation of Th1 responses and define the outcome of protective immunity during pulmonary tularemia. Similarly, in a sub lethal pulmonary tularemia infection model, the IL-17 gene deficient mice had delayed clearance of *F. tularensis* LVS suggesting a crucial role for IL-17 in protective immunity against this pathogen.[33] Consistent with the pulmonary tularemia model, studies with a pulmonary *C. muridarum* infection model have demonstrated that blocking IL-17 responses during infection results in increased susceptibility to infection.[26,43] One mechanism by which IL-17 can modulate adaptive response to Chlamydia was shown to be mediated via induction of IL-12 responses and driving Th1 responses.[26] However, it is likely that the impaired neutrophilic recruitment seen in both the pulmonary tularemia[15] and Chlamydia infection[43] may also contribute to protection. These studies suggest that IL-17 can regulate the adaptive Th1 immune response by modulating the production of Th1 polarizing cytokines by APCs and contribute to Th1 immunity and protection (**Fig. 1B**).

The above studies suggest an unique requirement for the IL-23-Th17 cell pathway in induction of Th1 cell responses during *F. tularensis* LVS,[15] *M. bovis BCG*[8] and *C. muriduram*[26] but not other intracellular infections such as *M. tuberculosis* (**Table 1**).[7] Since these different bacteria use a variety of specific PRR signaling, it is likely that they stimulate the production of distinct polarizing cytokines that influences subsequent adaptive immune responses. We propose that some intracellular bacterial infections can effectively induce IL-12-IFNγ responses in the host, while other pathogens require the IL-23-IL-17 pathway for effective

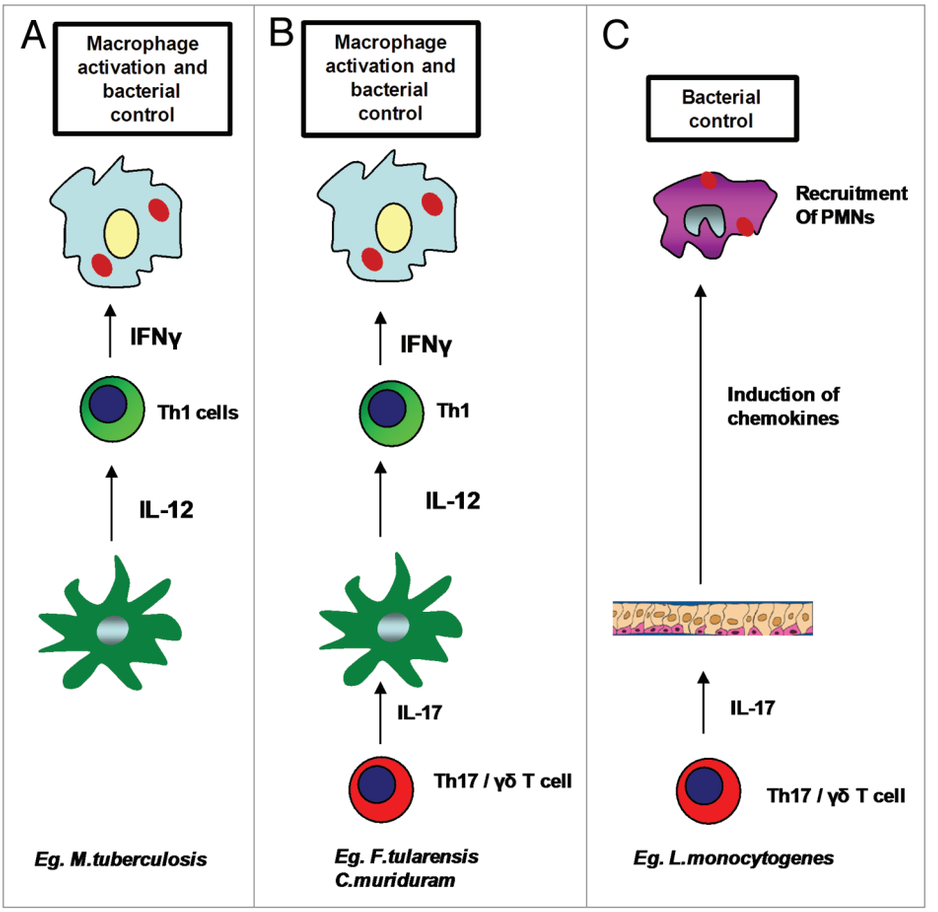

Figure 1. Role of IL-17 in protective immunity against intracellular pathogens. Involvement of Th17 pathway is not required for overall protective immunity against some intracellular pathogens such as *M. tuberculosis,* where activation of macrophages and bacterial killing takes place in the presence of functional IL-12 mediated Th1 responses (A). Th17 pathway is required for induction of IL-12 from DCs and generation of Th1 responses for macrophage activation and bacterial control in some pathogens such as *F. tularensis* LVS and *C. muridarum* (B). Th17 pathway is required for recruitment of neutrophils and bacterial killing in intracellular pathogens such as *L. monocytogenes* and *S. typhimurium* (C).

induction of host IL-12-IFNγ responses for intracellular pathogen control.

Intracellular Pathogens that may Require IL-17-dependent Neutrophilic Recruitment for Protective Immunity

Intracellular pathogens that require neutrophilic contribution to mediate protective immunity are dependent on the IL-23/IL-17 axis for induction of neutrophil attracting chemokines (**Fig. 1C**). IL-17 induces granulopoietic factors such as Granulocyte colony-stimulating factor (G-CSF) as well as CXC- chemokines such as CXCL-1, CXCL-2, CXCL-5 and CXCL-8, therefore implicating a crucial role for IL-17 in generation and recruitment of neutrophils in response to inflammation and infection (reviewed in ref. 9). Accordingly, induction of IL-17 and IL-17F production following acute *Mycoplasma pneumonia* pulmonary infection is IL-23-dependent and is required for neutrophil recruitment and protective immunity against this intracellular pathogen.[44] Neutrophils are a critical component of protective immunity against the gram positive intracellular bacteria *L. monocytogenes*. Accordingly, IL-23KO mice and IL-17RKO mice are more susceptible to *L. monocytogenes* infection and have reduced neutrophil recruitment to the liver.[31,45] γδ T cells and αβ TCR $CD4^-$ $CD8^-$ DN cells are documented to produce IL-17 during the early phase following *L. monocytogenes* infection and regulate the recruitment of neutrophils[31,45] and formation of granulomas.[45] Importantly, reconstitution of IL-17 by cytokine therapy[31] or adoptive transfer of αβ TCR $CD4^-$ $CD8^-$ IL-17 producing cells[30] reduced bacterial burden, confirming a role for IL-17 in protective immunity against *L. monocytogenes*.

Studies using the intracellular pathogen *S. typhimurium* have also shown that IL-17 and IL-22 are induced in the ileal mucosa in response to infection.[46] Absence of IL-23 and IL-17R signaling resulted in reduced induction of chemokines Macrophage inflammatory protein-2 (MIP-2) and keratinocyte-derived chemokine (KC) as well as anti-microbials, reduced neutrophilic recruitment to the ileal mucosa and increased dissemination of the bacteria to the lymph nodes.[29,46]

Similar observations were also seen in the *C. muridarum* pulmonary infection model where IL-17 was required for the induction of chemokines and recruitment of neutrophils for bacterial control.[43,47] These studies show that IL-17 made by

Table 1. Involvement of IL-17 in protective immunity to intracellular pathogens

Organism	Effect of lack of Th17 pathway	References
M. tuberculosis	Impacts inflammation, but not required for overall protection	5, 7
M. bovis BCG	Impacts formation of granulomas, but not required for overall protection	8, 35
S. enterica	Not required for protection	39
F. tularensis LVS	Increased susceptibility due to impaired Th1 responses	15
C .muriduram	Increased susceptibility due to impaired Th1 responses	26
L. monocyto-genes	Increased susceptibility due to impaired neutrophilic recruitment	31, 45
S. typhimurium	Increased dissemination due to impaired neutrophilic responses	29, 46
C. muriduram	Increased susceptibility due to impaired neutrophilic responses	43, 47

both Th17 cells and γδ T cells[29,48] may have an important role in immunity against intracellular infections by mediating the induction of chemokines required for neutrophilic recruitment and the control of bacteria.

Summary and Outlook

Our current understanding on the role of IL-17 and Th17 cells in the protective immunity to intracellular pathogens is evolving rapidly. Although initial studies in the mycobacterial infection models suggested that IL-17 was not required for protection, more recent studies have provided new insights into how IL-17 can regulate both innate and adaptive responses against other intracellular pathogens. Further studies to determine which PRRs used by intracellular pathogens trigger specific Th1 and Th17 polarizing cytokines will be critical in understanding why some, but not all intracellular pathogens require IL-17 for protective immunity.

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